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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,849	12/21/2001	Walter Callen	DIVER1350-5	9611

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	13

DATE MAILED: 06/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,849	CALLEN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication app ars on the cover she t with the correspondence address --

Period for R ply

. A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9&12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1 and 2 are pending.

2. Applicant's IDS, filed 10/2/02 and 2/4/03 (Paper No. 9 and 12, respectively), is acknowledged, however, reference AD was crossed as the entire document was not found. Applicant is invited to produce such documents.

3. The specification on page 1 should be amended to reflect the status of parent application No. 09/391,340.

4. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figure 1A through 1E, on page 6, lines 4-5 has described two sequences, nucleotide and deduced amino acid of DNA polymerase (IPY2) that each must have a sequence identifier. Correction is required.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. The phrase "polypeptides of SEQ ID NO:2" recited in claim 2, line 2, is indefinite because there is only one polypeptide of SEQ ID NO: 2.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody which specifically binds SEQ ID NO: 2 for screening assay, does not reasonably provide enablement for any purified antibody that specifically binds any polypeptide "having" "sequences substantially identical" to a sequence as set forth in SEQ ID NO:2 in claim 1, or any purified anybody that specifically binds to a polypeptide "having" "at least 10 consecutive amino acids" of the polypeptides as set forth in SEQ ID NO:2, and "sequences substantially identical thereto" in claim 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There is insufficient guidance and direction as to make and use antibodies, wherein the antibodies bind "sequences substantially identical to SEQ ID NO:2; at least 10 consecutive amino acids of the polypeptides as set forth in SEQ ID NO:2, and sequences substantially identical to at least 10 consecutive amino acids of the polypeptides as set forth in SEQ ID NO:2.

Claims 1 and 2 require antibody to bind to different polypeptides. However, the present specification fails to provide sufficient disclosure of amino acid fragments that maintain the structural and functional properties of the high temperature polymerase activity set forth in SEQ ID NO:2, wherein the fragment is immunogenic, or polypeptides at least 10 consecutive amino acids of SEQ ID NO: 2 or fragments substantially identical to at least 10 consecutive amino acids fragments which include numerous changes and variation. The specification does not provide sufficient guidance as to which of the amino acids may be changed while polymerase functional activity is retained. In addition, the term "having" in claims 1 and 2, respectively is open-ended, it expands the "sequences substantially identical" to a sequence as set forth in SEQ ID NO:2, the "at least 10 consecutive amino acids" and "sequences substantially identical" to "at least 10 consecutive amino acids" of the polypeptides as set forth in SEQ ID NO:2 to include additional non disclosed amino acids.

The one of the uses of the claimed polypeptide is to make antibody then any change in the polypeptide of SEQ ID NO: 2 would affect the binding specificity of the antibody. Colman *et al* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Futher, Lederman *et al* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document).

Because of this lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at the claimed fragments having galactosadase activity; its immunogenic fragments, at least 10 consecutive amino acids or sequences substantially identical thereto encompassed by the claimed invention.

The scope of the claimed antibodies that is specifically bind to SEQ ID NO:2 is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of amino acid sequences broadly encompassed by the claimed invention as recited in the claims 1 and 2. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's or peptide's amino acid sequence and still retain similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any,

are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a limited number of proteins and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

9. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an antibody that specifically binds SEQ ID NO: 2.

Applicant is not in possession of any purified antibody that specifically binds any polypeptide "having" "sequences substantially identical" to a sequence as set forth in SEQ ID NO:2 in claim 1, or any purified anybody that specifically binds to a polypeptide "having" "at least 10 consecutive amino acids" of the polypeptides as set forth in SEQ ID NO:2, and "sequences substantially identical thereto" in claim 2.

Applicant has disclosed only amino acid of SEQ ID NO: 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons

of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,491,086 (IDS Ref. # AG), as is evidenced by Bost et al. and Bendayan.

The `086 patent teaches an antibody that binds to peptides designed from Pyrodictium DNA polymerase (see column 13, lines 52-56 in particular), wherein Pyrodictium DNA polymerase has 71% identity to claimed SEQ ID NO:2 (see sequence alignment in particular). The patented Pyrodictium DNA polymerase having several fragments of at least 10 consecutive amino acids that are 100% identical to fragments of claimed polypeptide of SEQ ID NO: 2. The fragments are encompassed within 803 amino acid sequence and is included because "having" in the instant claims opens the claims up to include additional unrecited elements even in large amounts. Further, antibodies "cross-react" with antigens with homolgous amino acid residues. Further, the patented Pyrodictium DNA polymerase is considered substantially identical to SEQ ID NO: 2. Although the `086 patent does not teach specific amino acid sequence of SEQ ID NO:2, binding to "SEQ ID NO:2" is considered an inherent property of the reference antibody.

As is evidenced by Bost *et al* that an antibody "cross-reacts", i.e. binds to more than one protein sequence, which mean that "specifically bind" with both proteins. Bost et al (Immuno. Invest. 1988 ;17:577-586) describe antibodies which "cross-react" with IL-2 and HIV envelope protein, but establish that the binding of each protein is due to the presence of a homologous sequence in each protein in which 4-6 residues were identical (see entire document, especially the Abstract and Discussion).

Similarly, Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon

conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

Since the office does not have a laboratory to test the reference antibodies, it is applicant's burden to show that the reference antibody does not bind to the SEQ ID NO:2 recited in the claims. See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uemori et al (J. Bacteriol. 177:2164-2177, 1995), in view of Alisa Campbell (General properties and applications of monoclonal antibodies, Elsevier Science Publishers, 1984, section 1.1).

Uemori *et al* teach the polypeptide that is substantially identical that is 71% of claimed SEQ ID NO: 2 (see sequence alignment, Fig 3 page 2167 in particular). Uemori *et al* further teach the highly conserved sequence VIYGDTD (corresponding to amino acids 574-580 of SEQ ID NO:2) which is responsible for DNA synthesis and is important for the catalysis of DNA polymerization and dNTP binding (see Fig 1, page 2165 and page 2169 under Results and Discussion in particular). Further, the Uemori *et al* referenced polypeptide having several fragments of at least 10 consecutive amino acids that are 100% identical to fragments of claimed polypeptide of SEQ ID NO: 2, such as the highly conserved sequence VIYGDTD (see sequence alignment in particular). Finally, Uemori *et al* teach that DNA polymerase is one of the most important enzymes for living cells (see column 1, line 45-48 in particular).

The claimed invention differs from the reference teachings only by the recitation of a purified antibody which specifically binds to a polypeptide having sequences substantially identical to SEQ ID NO:2 in claim 1; a purified antibody that specifically binds to a polypeptide having at least 10 consecutive amino acids of the polypeptide of SEQ ID NO: 2 and sequences substantially identical thereto in claim 2.

Campbell teaches that it is customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (see page 3 figure 11.1 in particular). One field of research in which monoclonal antibodies may prove of particular value is in the study of chromosomal proteins. The search for those chromosomal proteins which are responsible for determining cell phenotype has been particularly long and comparatively fruitless and monoclonal antibodies are ideal tools for the dissection of the complex mixture of proteins. As hybridoma production becomes a more routine laboratory technique (see page 29 and 30 under Basic research in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an antibody as taught by Campbell against the polypeptide of the DNA polymerase taught by the Uemori *et al* reference.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was customary at the time the invention was made to make monoclonals against any new macromolecule as taught by Campbell, wherein the such DNA polymerase is one of the most important enzymes for living cells, and further, the DNA polymerase contains highly conserved sequence which is responsible for DNA synthesis and is important for the catalysis of DNA polymerization and dNTP binding as taught by the Uemori *et al* reference.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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June 16, 2003

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